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Iridium-catalyzed triple C(sp^3)–H borylations: construction of triborylated sp^3-carbon centers†

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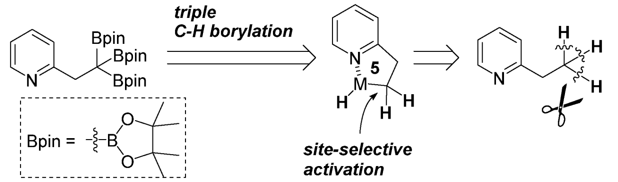
An unprecedented catalytic C(sp^3)–H triborylation at a single carbon was developed with the assistance of a nitrogen directing group.

Triborylated compounds possessing three boron atoms on the same carbon are extremely unique, exhibiting interesting reactivities toward many electrophiles.[1b] For the preparation of these fascinating molecules, traditional methods employed either triborylations of the corresponding trihalides[1a,b] or hydroborations of alkenes, borylalkynes, and borylalkenes with/without a transition metal catalyst.[1c–f] However, the product yields of triborylated compounds were not satisfactory, and regioselective introduction of boron atoms into unsymmetrical double bonds was often problematic.[1c,f] Therefore, we devised a new synthetic method based on a stable five-membered metallacycle intermediate (Scheme 1). If a nitrogen atom is located at an appropriate position, C(sp^3)–H bond cleavage would proceed concomitantly with the five-membered chelation with a transition metal.[2] Therefore, with a highly reactive borylating reagent, B_2pin_2, site-selective C(sp^3)–H borylation of 2-ethylpyridine would be possible at the terminal position, eventually leading to triborylated products. This strategy would avoid multiple borylations at two vicinal sp^3-carbons.

A transition metal-catalyzed C(sp^3)–H borylation is an advanced technology for preparing borylated compounds from simple alkanes. Since Hartwig developed C(sp^3)–H borylation promoted by transition metal complexes in 1997,[3a] photo and thermal catalytic methods using B_2pin_2 or HBpin have been established.[3] Although most of the methods have been limited to borylations of terminal C(sp^3)–H bonds,[3,4] several new methods that promote borylation of secondary C(sp^3)–H bonds with high efficiency have recently been developed.[5,6] Among these methods, double C(sp^3)–H borylation at a single carbon sometimes proceeded to produce geminal diborylated compounds,[4a,6] but C(sp^3)–H triborylation has not been reported thus far, even though it would have been an undesired pathway. We herein disclose the first and robust synthesis of triborylated products by triple borylation of terminal primary C(sp^3)–H bonds with the aid of a nitrogen directing group such as a pyridine as well as an isoquinoline.



Scheme 1 Our synthetic strategy for triple C(sp^3)–H borylation.

According to our previous report on iridium-catalyzed C(sp^3)–H silylation reaction,[7] we employed $[Ir(cod)Cl]_2$ as a catalyst without any additional ligands. Aiming at the selective generation of triborylated compounds, an excess amount of B_2pin_2 was employed for the borylation of 2-ethylpyridine (**1a**) using *n*-octane as a solvent under reflux conditions (bath temp: 150 °C) (Table 1). When 1.5 equiv. of B_2pin_2 was used, **1a** was consumed within 1.5 h and mono-, di-, and triborylated products **2a**, **3a**, and **4a** were obtained in 10%, 22%, and 19% yields, respectively (entry 1). Although C(sp^2)–H bonds of the pyridine ring were over-borylated (**5a** and **6a**), the total yield of the triborylated compounds was 34% (**4a**: 19%; **5a**: 10%; **6a**: 5%). Increased use of B_2pin_2 led to improvement in the total yield (entries 2 and 3). Eventually, both **5a** and **6a** were produced in total 91% yield by using 3.5 equiv. of B_2pin_2 (entry 4). In this nitrogen-directed borylation, a bidentate amine ligand for an iridium center such as 3,4,7,8-tetramethyl-1,10-phenanthroline[3f,4c,5] was not effective, yielding a complex mixture (entry 5).

The triborylated compound **4a** was isolated in 17% yield (Table 1, entry 2) by silica gel column chromatography (using pre-dried SiO_2: 63–210 μm; eluent: hexane–AcOEt containing 3% of Et_3N), and the solids thus obtained were crystallized from hexane at rt to afford an appropriate grade of a single crystal. X-ray crystal analysis of **4a** confirmed its exact structure, in which three pinacolborons were attached to a single carbon (Fig. 1).[8] The nitrogen atom of the pyridine ring coordinated to one of the three boron atoms and the

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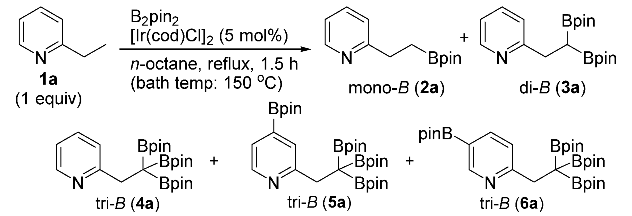
Table 1 Screening of the amount of B_2pin_2



Entry	B_2pin_2 (equiv.)	Yield[a] (%) 2a	3a[b]	4a	5a	6a
1	1.5	10	22	19	10	5
2	2	4	13	20 (17)	24	10
3	3	<1	<1	<1	66	19
4	3.5	<1	<1	<1	71	20
5[c]	3.5	Complex mixture				

[a] Yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The value in parentheses represents isolated yield. [b] In entries 1–4, C(sp^2)–H borylation products of **3a** (4- and 5-positions) were observed in total *ca.* 10% yield. [c] 10 mol% of 3,4,7,8-tetramethyl-1,10-phenanthroline was added.

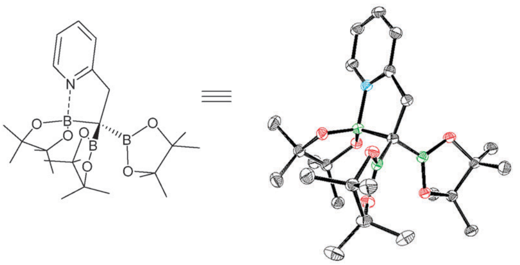


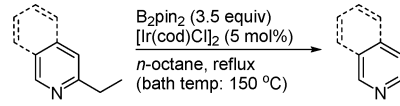
Fig. 1 ORTEP structure of **4a**. Thermal ellipsoids are given at the 50% probability level. Hydrogen atoms are omitted for clarity.

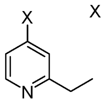
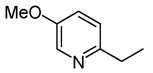
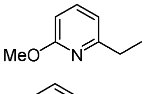
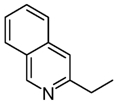
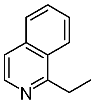
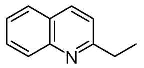
length of N–B was 1.660 Å, suggesting that coordination of the nitrogen atom stabilized triborylated compounds.

Based on these observations, we next investigated the effects of substituents at the 4-position of the pyridine, which might affect the nucleophilic property of the pyridine nitrogen. Additionally, one substitution on the pyridine ring might suppress over-borylation of aromatic C(sp^2)–H bonds due to the steric repulsion against an introduced substitution.

Several 2-ethylpyridine derivatives bearing electron-withdrawing and donating substituents at the 4-position of the pyridine ring were prepared and subjected to borylation (Table 2). Triborylated products obtained by this procedure were not so stable in silica gel column chromatography, and some decomposition occurred during the purification process. Electron-withdrawing substituents such as nitro, cyano, and chloro (**1b**, **1c**, and **1d**) did not effectively promote triborylation even with extended reaction time, while the use of electron-donating substituents such as Me, OMe, and OBn (**1e**, **1f**, and **1g**) resulted in completion of triborylation within 10–30 min with sufficient suppression of over-borylation of aromatic C(sp^2)–H bonds (less than 2%): triborylated compound **1g** was obtained in 99% yield after only 10 min (isolated yield of 64%). In addition, triborylation of 5-OMe-2-ethylpyridne (**1h**) also proceeded with high conversion, but that of the 6-OMe-derivative (**1i**) did not, probably because *ortho*-substitutions of the pyridine ring prevented coordination of the nitrogen atom to metals (Ir and B). Furthermore, reactions of 3- and 1-ethylisoquinolines (**1j**, and **1k**) gave moderate yields with diborylated compounds remaining. Sterically crowded 2-ethylquinoline (**1l**) was less reactive than other substrates and only 2% of the triborylated product was observed. Based on these experimental results, we concluded that the lone pair of nitrogen had an important effect on triborylation: electron-rich nitrogen atoms with less steric bulkiness caused high conversion probably due to the facilitation of iridacycle formation in addition to stabilization of the corresponding triborylated compounds.

Table 2 Scope and limitations

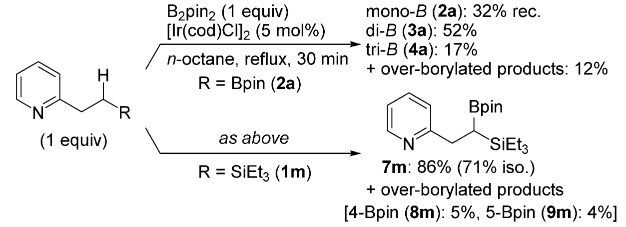


Entry	Substrate	Time (h)	Yield[a] (%) tri-B (4)	di-B (3)	mono-B (2)
1	 X = NO_2 (**1b**)	13	1	8	20
2	= CN (**1c**)	13	1	5	16
3	= Cl (**1d**)	0.5	12	25	18
4	= Me (**1e**)	0.5	96 (75)	<1	<1
5[b]	= OMe (**1f**)	0.2	95 (81)	<1	<1
6	= OBn (**1g**)	0.2	99 (64)	<1	<1
7[c]	 **1h**	0.5	89 (77)	3	<1
8[d]	 **1i**	1.5	<1	<1	<1
9[e]	 **1j**	0.5	77 (52)	7	<1
10[f]	 **1k**	1.0	57 (44)	22	<1
11	 **1l**	1.5	2	8	21

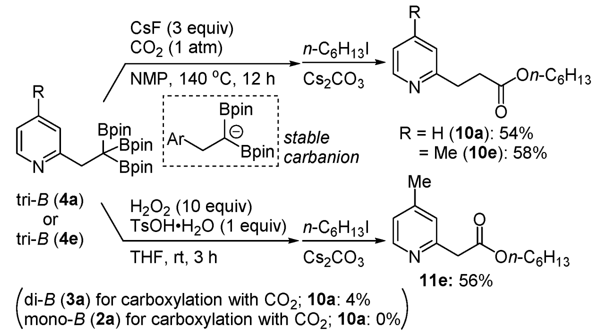
[a] Yields were determined by ^{1}H NMR analysis. The values in parentheses represent isolated yields. [b] C(sp^2)–H borylation product of **4f** (5-position) was obtained in 2% yield. [c] C(sp^2)–H borylation product of **4h** (4-position) was obtained in 7% yield. [d] C(sp^2)–H borylation products of **1i** (4- and 5-positions) were observed in 31% total yield. [e] C(sp^2)–H borylation products of **4j** (positions not determined) were obtained in 14% total yield. [f] C(sp^2)–H borylation products of **4k** and **3k** (positions not determined) were obtained in 9% and 10% yields, respectively.

We next investigated borylation of secondary C(sp^3)–H bonds since this triborylation is thought to proceed in a stepwise fashion from a monoborylated compound *via* secondary followed by tertiary C(sp^3)–H bond activations. To prove this hypothesis, monoborylated compound **2a** was employed for further borylation with B_2pin_2. As a result, **2a**, **3a**, and **4a** were obtained in 32%, 52%, and 17% yields, respectively, suggesting that triborylation actually proceeded in this stepwise manner (Scheme 2).[9]

Alkylsilane **1m** was also monoborylated to afford **7m** in 86% yield (isolated yield of 71%) along with a small amount of over-borylated products **8m** and **9m**. Since the borylation of 2-propylpyridine gave a complex mixture under the same conditions (no scheme),



Scheme 2 Borylation of secondary C(sp^3)–H bonds.



Scheme 3 Carboxylation and oxidation of triborylated compounds.

these studies indicate that C(sp^3)–H bonds next to a metalloid atom (Si, B) are easily borylated probably due to their relatively acidic nature.[10]

We were then interested in the reactivities of triborylated compounds and potential transformations were tested. We have already reported a fluoride-mediated carboxylation of benzylic C(sp^3)–Sn and –Si bonds with CO_2[11] using CsF as a mild activator.[7,12] This novel strategy could be applied to carboxylation of triborylated compounds because fluoride has been reported to efficiently activate pinacolborates.[13] Indeed, isolated products **4a** and **4e** were subjected to carboxylation under 1 atm of CO_2 in the presence of CsF, giving the carboxylated products **10a** and **10e** in 54% and 58% yields, respectively, after esterification with n-C_6H_{13}I (Scheme 3).[14] Neither dicarboxylic nor tricarboxylic acids were observed. Trioxidation of **4e** was also examined using H_2O_2 in the presence of an acidic additive such as TsOH·H_2O in order to avoid base-promoted protodeborylation. As a result, one carbon-shortened carboxylic acid derivative **11e** was obtained in 56% yield. These two methods are complementary because different chain lengths of carboxylic acids can be prepared only by changing the reagents employed. When di- and monoborylated compounds **3a** and **2a** were used as substrates for fluoride-mediated carboxylation with CO_2, **10a** was obtained in 4% and 0% yields,[15] strongly indicating that the generation of a carbanion was facilitated by its delocalization with vacant p-orbitals of the remaining two boron atoms.

In summary, we have developed iridium-catalyzed triborylation reactions of terminal C(sp^3)–H bonds. Electron-donating substituents on the pyridine ring with less steric bulkiness enhanced the production of triborylated compounds (up to 99% yield). The products thus obtained were successfully transformed into carboxylic acid derivatives under 1 atm of CO_2 in the presence of CsF as well as under oxidative conditions.

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